REMARKS

Claims 1-6, 8-9, 11, and 14-15 are presently pending in the captioned application. The amendments are presented in the expectation that the amendments will place this application in condition for allowance. The amendments were made, in accordance with the Examiner's suggestions, to further specify that the claimed inclusion complexes, compositions, and methods be solely used for oral administration. Additionally, applicants have amended claim 1 to specify that the claimed inclusion complexes do not contain an acid component. As already indicated by the Examiner in the Advisory Action, the original specification as filed provides support for this amendment at page 4, lines 15-17. The amendments do not introduce new matter within the meaning of 35 U.S.C. § 132. Accordingly, entry of the amendments is respectfully requested.

1. Rejection of claims 1-9, 11, 14, and 15 under 35 U.S.C. § 103

The Advisory Action states that the previous rejections of claims 1-9, 11, 14, and 15 under 35 U.S.C. § 103 as being obvious are maintained. In particular, the Advisory Action affirms the Final Office Action rejection of claims 1, 2, 5-9, 11, and 14 over Nath et al. (Novel Met-Enkephalin Analogue, Pharm. Res. Vol. 31, No. 5, pages 269-273 (1995)) in view of Chiesi et al. (U.S. Patent No. 5,855,916); claims 1-3, 7-9, and 11 over European Patent

Application No. 0 463 653 ("'653") in view of Nath et al.; claims 1, 2, 4, 7-9, 11, and 14 over Hora et al. (U.S. Patent No. 5,977,856) in view of Nath et al.; and claims 1, 7-9, 11, and 15 over French Patent 2 710 268 ("'268") in view of Nath et al.

Applicants respectfully traverse this rejection because all three prongs for a *prima facie* case of obviousness have not been established for each of the rejections. Specifically, all the claim limitations are not present in the cited references and one of ordinary skill in the art would have had no motivation to modify the cited references into the present invention.

To establish a *prima facie* case of obviousness, the Examiner must establish: (1) that some suggestion or motivation to modify the references exists; (2) a reasonable expectation of success; and (3) that the prior art references teach or suggest all the claim limitations. In re Fine, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); Amgen, Inc. v. Chugai Pharm. Co., 18 USPQ2d 1016, 1023 (Fed. Cir. 1991); In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970).

A *prima facie* case of obviousness must also include a showing of the reasons why it would be obvious to modify the references to produce the present invention. See Ex parte Clapp, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The Examiner bears the initial burden to provide some convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings. Id. at 974.

1. Rejection of claims 1, 2, 5-9, 11 and 14 over Nath et al. in view of Chiesi et al.

As a basis for maintaining this rejection the Advisory Action states:

> Chiesi et al's acid component would not materially affect the basic and novel characteristics of Applicants' claimed composition because Chiesi et al's acid component is useful in improving the storage stability, the water solubility, and the bioavailability of compositions which can be orally administered. These characteristics and functions are fully consistent with the basic and novel characteristics of Applicants' claimed compositions. If Applicants intend to exclude an acid component from their claimed compositions, Applicants may wish to consider inserting claim limitations which explicitly exclude such a component. Page 4, lines 15-17, of Applicants' specification may constitute written descriptive support for such a negative claim limitation. Such a limitation would overcome the rejection based upon the Nath et al article in view of Chiesi et al.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and every limitation of the presently claimed invention.

In accordance with the Examiner's suggestions, applicants have amended presently pending claim 1 to specify that the claimed inclusion complexes do not contain an acid component. In view of the Examiner's statement that "Such a limitation would overcome the rejection based upon the Nath et al article in view of Chiesi et al.", applicants respectfully request the Examiner to reconsider and withdraw the instant rejection.

In this regard, applicants note that Chiesi et al. disclose multicomponent inclusion complexes containing a basic-type drug, a

cyclodextrin, and an acid as the essential components. Chiesi et al. teach that the acid is the critical component to establishing the water solubility of the inclusion complexes. In fact, Chiesi et al. specifically disclose "the present invention relates to the use of an acid in the preparation of complexes with a cyclodextrin...with the purpose of increasing the water solubility of the cyclodextrin itself." (See column 2, lines 8-12). Chiesi et al. provide no teaching for inclusion complexes that do not contain an acid as an essential component.

In contrast, applicants' claims as presently amended are limited to inclusion complexes containing an opioid peptide and a cyclodextrin derivative as the only essential components in a molar ratio of 1:5 to 2:1 and specifically exclude an acid component. Neither reference cited by the Examiner teaches inclusion complexes having only these two essential components, and no acid component, in the specified molar ratio. Nath et al. merely teach a particular compound by itself, without inclusion of a cyclodextrin derivative. Likewise, Chiesi et al. teach inclusion complexes which require a basic-type drug, a cyclodextrin derivative, and an acid. The acid is a critical component of the inclusion complexes taught by Chiesi et al. since Chiesi et al. disclose that the acid itself provides the desired increase in water solubility. In contrast, the presently claimed inclusion complexes do not contain an acid to increase water solubility.

The basic and novel characteristic of the presently claimed invention relates to an inclusion complex effective for oral administration (i.e. water soluble) based solely on a molar ratio of 1:5 to 2:1 of a specific opioid peptide and a cyclodextrin derivative. An additional acid component is specifically excluded from the claimed inclusion complex.

Additionally, a person of ordinary skill in the art would recognize that the opioid peptide used according to the presently claimed invention is already soluble in water and stable. Accordingly, this peptide does not require improved water solubility or stability. The presently claimed invention, then, is patentably distinct from the references cited by the Examiner. A person of ordinary skill in the art would have had no reasonable expectation of success in forming orally available inclusion complexes containing only the presently claimed specific peptide as well as a cyclodextrin as the only essential components, without an additional acid, as required by Amgen, Inc. v. Chugai Pharm. Co.

Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of Chiesi et al. and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1, 2, 5-6, 8-9, 11, and 14.

2. Rejection of claims 1-3, 7-9, and 11 over EP '653 in view of Nath et al.

As a basis for maintaining this rejection the Advisory Action states:

> The European Patent application 463,653's preference for nasal administration does not prevent the rejection of Applicants' claims, which embrace nasal administration (see claim 11). In any event, the European Patent Application '653 teaches oral administration at column 7, lines 16-17. The examiner does not question that Applicants' compositions are effective for oral administration; however, Applicants have not supplied any evidence contradicting the statement at column 7, lines 16-17, that the compositions of the European Patent Application '653 are effective oral administration. Concerning the data set forth at page 13 of Applicants' response, the data can not be relied upon to establish criticality for the claimed molar ratio range because the data was not submitted in appropriate form under 37 CFR 1.132. Further, even if submitted in the form of an affidavit or declaration under 37 C.F.R. 1.132, it is not clear that the data would be sufficient to rebut the prima facie case of obviousness because the data does not indicate what peptide was tested, the data does not test the specific cyclodextrin derivatives taught by Chiesi et al, and the data does not test molar ratios both within and outside of Applicants' claimed range (see MPEP 716.02(d) under "Demonstrating Criticality of a Claimed Range"). The submitted data is also not commensurate in scope with the rejected claims, and especially with claims 11 and 15, which do not require oral administration. Finally, Applicants' argument that the currently claimed molar ratio is "essential" for biological activity after oral administration is contradicted by the fact that the original disclosure indicates that the range is preferred, not "essential". Note the lack of any such range, e.g., in originally filed claim 1.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and

every limitation of the presently claimed invention.

The presently claimed invention relates to novel inclusion complexes consisting essentially of an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative as the sole essential components in a molar ratio of 1:5 to 2:1. These complexes are formulated for oral administration and prolong the duration of action of the active agent. Further, these complexes do not contain an acid component.

In contrast, Nath et al. teach the compound Tyr-D-Ala-Gly-MePhe-Gly-NHC_3H_7. Nath et al. do not disclose inclusion complexes containing the embodied compound in combination with a cyclodextrin derivative, let alone inclusion complexes in a molar ratio of 1:5 to 2:1 formulated for oral administration, as required by the presently pending claims. Accordingly, Nath et al. do not teach each and every limitation of independent claim 1.

EP '653 does not remedy these deficiencies. EP '653 teaches combining drugs including peptide drugs such as enkephalins with an enhancer of absorption at a mucosal surface and a cyclodextrin. The reference further teaches that undesirable side-effects due to using an absorption enhancer alone may be avoided when an absorption enhancer is used in combination with a cyclodextrin to permit nasal administration. See Column 3, lines 9-15.

Further, as noted by the Examiner in the Official Action dated February 3, 2003, the combination disclosed by EP '653 "permits the drugs to be administered nasally, thereby avoiding the problems of poor absorption after oral administration and avoiding undesirable metabolism of the drugs." Accordingly, as the Examiner has admitted on the record, the combinations disclosed by EP '653 are preferably administered nasally since they show poor oral efficacy.

Additionally, EP '653 provides no teaching that opioid peptides, such as the opioid peptide according to the presently claimed invention, are included among the drugs used in the disclosed medicaments. Further, the absorption enhancers are necessary to increase the permeability of the nasal mucosa in order to enable the disclosed intranasal administration. See column 1, lines 52-58.

In contrast, the presently claimed invention relates to inclusion complexes having a long duration of activity and improved efficacy that are specifically formulated for oral administration. Accordingly, the presently claimed inclusion complexes cannot be administered intranasally. The presently claimed invention, then, is entirely different from the EP '653 disclosure, relating to nasal administration of cyclodextrin to avoid the problems of poor absorption after oral administration and to avoid undesirable

metabolism of drugs.

Applicants acknowledge the Examiner's indication that "European Patent Application '653 teaches oral administration at column 7, lines 16-17." However, the EP '653 reference is non-enabling for such an oral administration. In fact, the EP '653 reference on its face teaches away from oral administration, stating at col. 1, lines 11-15 that the disclosed nasal administration was "proposed as an alternative to oral administration in cases where drugs are only absorbed poorly by an oral route or are extensively metabolized in the gastrointestinal tract or subjected to first-pass metabolism in the liver." (Emphasis added).

The presently claimed inclusion complexes are formulated for delivery to a patient solely via an oral route. The enzymes and environment involved in oral and nasal administrations are totally different. Accordingly, the presently claimed invention, directed to oral administration solely, is entirely different than the disclosure of the EP '653 reference, directed to nasal administration. EP '653 specifically requires the nasal route to avoid a first pass effect exhibited when using an oral administration of the disclosed ingredients. Accordingly, one of ordinary skill in the art would have no basis to believe that the

formulations of the EP '653 reference could be effectively administered orally in view of a lack of an enabling disclosure in this regard.

Moreover, the EP '653 reference repeatedly refers to examples of a cyclodextrin complex of the surfactant Laureth-9. The EP '653 reference does not provide any practical demonstration showing active drug substances that may effectively be used in this complex. Additionally, while cols. 5 and 6 of the EP '653 reference disclose several proteins and peptides that can be used in the disclosed compositions, for example insulin, gentamicin, glucagons, growth hormone, calcitonins and synthetic modifications thereof, enkephalins, interferons, etc., the reference does not in any way disclose using any opioid peptide in these compositions, let alone the specific opioid peptide required by the presently pending claims. Accordingly, a person of ordinary skill in the art would have had no motivation to combine the EP '653 reference with the Nath et al. reference to arrive at the presently claimed invention. The EP '653 reference, on its face, does not support the Examiner's assertion that the disclosed compositions are capable of effectively orally administering a specific opioid to a patient.

While EP '653 does provide an example of a cyclodextrin

complex with Laureth-9 and states that any active drug substance may be used in the embodied compositions, the reference does not actually provide any practical demonstrations, in the form of Examples or otherwise, regarding the disclosed drugs. Accordingly, this reference is non-enabling for the combination asserted by the Examiner. In re Wiggins, 179 USPQ 421, 425 (C.C.P.A. 1973).

By combining the requirement of a specific opioid peptide with the requirement of oral administration, the presently claimed inclusion complexes represent a significant improvement over the teachings of the EP '653 reference taken alone or in combination with Nath et al. The data in Tables 2 and 3 of the instant specification, at pages 14 and 15, support this assertion by demonstrating that the presently claimed inclusion complexes are effective via oral administration, a result not recognized by EP '653.

In sum, a person of ordinary skill in the art would have had no motivation to combine the references cited by the Examiner to arrive at the presently claimed invention as required by In re Fine in view of the fact that EP '653 teaches away from the presently claimed invention requiring a composition containing an opioid peptide that is orally administered.

Further, applicants claims as presently amended are limited to

inclusion complexes containing an opioid peptide and a cyclodextrin derivative in a molar ratio of 1:5 to 2:1 as the only essential components. Neither reference cited by the Examiner teaches inclusion complexes having only these two essential components. As shown above, Nath et al. merely teaches a particular compound by itself, without inclusion of a cyclodextrin derivative. Likewise, EP '653 teaches inclusion complexes which require a peptide drug, a cyclodextrin derivative, and an enhancer of absorption at a mucosal surface. The absorption enhancer is a critical component of the inclusion complexes taught by EP '653 since they are necessary for the enablement of the intranasal administration. In contrast, the presently claimed inclusion complexes do not contain an absorption enhancer.

Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of EP '653 and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1-3, 8-9, and 11.

3. Rejection of claims 1, 2, 4, 7-9, 11, and 14 are rejected over Hora et al. in view of Nath et al.

As a basis for maintaining this rejection the Advisory Action states:

> Applicants argue that column 25, lines 3-6, of Hora et al does not constitute an enabling disclosure for the formation of inclusion complexes. However, prior art references are presumed enabling, and Applicants have not

> submitted any evidence or scientific reasoning to support their assertion that one of ordinary skill in the art can not form inclusion complexes by following the disclosure of Hora et al.
> Concerning the data set forth at page 13 of Applicants' response, the data can not be relied upon to establish criticality for the claimed molar ratio range because the data was not submitted in appropriate form under 37 CFR 1.132. Further, even if submitted in the form of an affidavit or declaration under 37 C.F.R. 1.132, it is not clear that the data would be sufficient to rebut the prima facie case of obviousness because the data does not indicate what peptide was tested, the data does not test the specific cyclodextrin derivatives taught by Chiesi et al, and the data does not test molar ratios both within and outside of Applicants' claimed range (see MPEP 716.02(d) under "Demonstrating Criticality of a Claimed Range"). The submitted data is also not commensurate in scope with the rejected claims, and especially with claims 11 and 15, which do not require oral administration. Finally, Applicants' argument that the currently claimed molar ratio is "essential" for biological activity after oral administration is contradicted by the fact that the original disclosure indicates that the range is preferred, not "essential". Note the lack of any such range, e.g., in originally filed claim 1.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and every limitation of the presently claimed invention.

As stated above, the presently claimed invention relates to novel inclusion complexes consisting essentially of an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative as the sole essential components in a molar ratio of 1:5 to 2:1. These complexes are

formulated for oral administration and prolong the duration of action of the active agent. Further, these complexes do not contain an acid component.

In contrast, Nath et al. do not disclose inclusion complexes containing the embodied compound in combination with a cyclodextrin derivative, let alone inclusion complexes in a molar ratio of 1:5 to 2:1 formulated for oral administration, as required by the presently pending claims. Accordingly, each and every limitation of independent claim 1 is not taught by Nath et al.

Hora et al. do not remedy these deficiencies. Hora et al. disclose a method and compositions for stabilizing and/or solubilizing polypeptide drugs and proteins by means of a cyclodextrin to obtain improved solubility and stability. This is achieved by combining the polypeptide with an effective solubilizing and/or stabilizing amount of a cyclodextrin, i.e. placing the polypeptide in an aqueous solution of the cyclodextrin. This solution was proposed to the well-known problem of poor solubility of purified proteins and polypeptides due to the presence of quaternary and tertiary structures. This is recognized at col. 13, lines 17-20 of Hora et al., disclosing that the polypeptides "may possess unique conformations (combinations of secondary, tertiary and quaternary structure) which affect their biological function, aqueous solubility, and ability to interact

with the cyclodextrins."

In contrast, the presently claimed invention has overcome this recognized problem by using a small peptide, i.e. a penta-peptide, which is easily soluble in both aqueous and non-aqueous solvents and stable under ambient conditions. Accordingly, the compositions disclosed by Hora et al., related to stabilizing and/or solubilizing polypeptide drugs and proteins by means of a cyclodextrin to obtain improved solubility and stability, are not applicable and bear no relevance to the presently claimed inclusion complex requiring a specific opioid peptide. Accordingly, a person of ordinary skill in the art would have had no motivation to combine the composition of Hora et al. with the compound of Nath et al. to arrive at the presently claimed invention since the Nath et al. compound does not possess the stability and solubility problems Hora et al. proposed to solve.

In particular, Hora et al. have demonstrated their claims of improved stability and solubility with high molecular weight proteins such as IL-12, TNF, and mCSF. However, Hora et al. do not discloses smaller peptides, such as the specific opioid peptide included in the presently pending claims or any other synthetic modification of enkephalin molecules, as capable of realizing the benefits of the disclosed compositions.

Further, Hora et al. teach combining the polypeptide with an effective solubilizing and/or stabilizing amount of a cyclodextrin, i.e. placing the polypeptide in an aqueous solution of the cyclodextrin. As a result, the polypeptide merely exists within the cyclodextrin aqueous solution; no reaction occurs between the cyclodextrin and the polypeptide-each exists as a separate component.

In contrast, the presently claimed invention relates to inclusion complexes consisting essentially of a specific opioid peptide combined with a cyclodextrin derivative in a molar ratio of 1:5 to 2:1. Since the invention relates to inclusion complexes, it is inherent that the two components making up the complexes must react in some way to from the complexes. Accordingly, the resultant complexes represent an entirely new chemical entity as compared to the initial two components, sometimes even having a slight modification in the structure of these components in order to permit the inclusion complexes to be formed. Such complexes are neither disclosed nor even contemplated by the Hora et al. reference, which merely shows placing a polypeptide in an aqueous cyclodextrin solution. Since Hora et al. does not contemplate the use of both of the presently claimed starting components, the disclosure of Hora et al. cannot recognize the unique inclusion

complexes that are presently claimed.

Further, applicants have observed that the peptide L-Tyr-D-Ala-Gly-N-methylphenylalanyl-glycyl-isopropylamide combined with beta-cyclodextrin in a 1:2 ratio is more effective orally than a 1:1 ratio. It would not at all have been obvious in view of the Hora et al. and Nath et al. references that a cyclodextrin derivative enhances the stability, solubility, and bioavailability of opioid peptides delivered orally when used in the claimed ratio.

Further, in the case of transdermal delivery, the effectiveness of these complexes is reversed. Accordingly, the molar ratio of peptide to cyclodextrin is not "routinely determined and optimized by one skill in the art" as the Examiner previously alleged. Formation of the presently claimed inclusion complexes containing this specific opioid peptide and a cyclodextrin would not have been obvious to a person of ordinary skill in the art without some teaching in this direction by the cited references. Neither reference cited by the Examiner contains such a teaching. Accordingly, the references cited by the Examiner merely provide an invitation to experiment. These references do not predict that any drug can be combined with cyclodextrins to form orally effective pharmaceutical compositions, nor do they teach how opioid peptides will behave when combined with cyclodextrins.

Accordingly, a person of ordinary skill in the art would have had no motivation to combine these references to arrive at the presently claimed invention without impermissible hindsight. See In re Dembiczak, 50 USPQ2d 1614 (Fed. Cir. 1999). The presently claimed complexes were not achieved or suggested by the prior art given that the varying parameters and innumerable possibilities that would have had to be tried until the successful combination was arrived at. Since the prior art does not indicate which parameters are critical, or how the opioid can be expected to behave with cyclodextrin, the only direction as to which of the many choices is likely to be successful is impermissibly provided by the present application. "When a rejection depends on a combination of prior art references there must be some teaching, suggestion, or motivation to combine these references." In re Rouffet, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998). As stated herein, no such motivation is present in the cited references.

Regarding the Examiner's previous assertion that "Hora et al's description of the cyclodextrins as stabilizing polypeptides in order to maintain their activity...is synonymous with Applicants' desired results of long duration of activity and improved efficacy", this is incorrect. In particular, while the portion of the reference cited by the Examiner does relate to stabilizing

polypeptides, it does not disclose that such stabilization is performed in order to maintain the polypeptides activity. In fact, column 19, lines 48-50 implies that most solubilization/stabilization agents provide an "appreciable loss of activity" to the polypeptides which are being stabilized. Accordingly, Hora et al.'s description of the cyclodextrins as stabilizing polypeptides is not actually synonymous with applicant's claimed inclusion complexes having a prolonged activity.

Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of Hora et al. and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1, 2, 4, 8-9, 11, and 14.

4. Rejection of claims 1, 7-12, and 15 are rejected over French Patent '268 in view of Nath et al.

As a basis for maintaining this rejection the Advisory Action states:

> The Examiner has nowhere admitted that the French Patent '268 "teaches away" from Applicants' claimed complexes. Concerning the data set forth at page 13 of Applicants' response, the data can not be relied upon to establish criticality for the claimed molar ratio range because the data was not submitted in appropriate form under 37 CFR 1.132. Further, even if submitted in the form of an affidavit or declaration under 37 C.F.R. 1.132, it is not clear that the data would be sufficient to rebut the prima facie case of obviousness because the data does not

> indicate what peptide was tested, the data does not test the specific cyclodextrin derivatives taught by Chiesi et al, and the data does not test molar ratios both within and outside of Applicants' claimed range (see MPEP 716.02(d) under "Demonstrating Criticality of a Claimed Range"). The submitted data is also not commensurate in scope with the rejected claims, and especially with claims 11 and 15, which do not require oral administration. Finally, Applicants' argument that the currently claimed molar ratio is "essential" for biological activity after oral administration is contradicted by the fact that the original disclosure indicates that the range is preferred, not "essential". Note the lack of any such range, e.g., in originally filed claim 1.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and every limitation of the presently claimed invention.

As stated above, the presently claimed invention relates to novel inclusion complexes consisting essentially of an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative as the sole essential components in a molar ratio of 1:5 to 2:1. These complexes are formulated for oral administration and prolong the duration of action of the active agent. Further, these complexes do not contain an acid component.

In contrast, Nath et al. do not disclose inclusion complexes containing the embodied compound in combination with a cyclodextrin derivative, let alone inclusion complexes in a molar ratio of 1:5

to 2:1, as required by the presently pending claims. Accordingly, each and every limitation of independent claim 1 is not taught by Nath et al.

FR '268 does not remedy these deficiencies. FR '268 teaches combining various peptide hormones with a cyclodextrin. This combination permits the drugs to be administered transcutaneously. In fact, FR '268 relates solely to transdermal preparations of cyclodextrin complexes of various drugs. Indeed, as the Examiner has admitted, FR '268 teaches that transcutaneous administration is used as an alternative to oral administration to "avoid problems of poor absorption after oral administration". Additionally, FR '268 provides no teaching that opioid peptides, such as the opioid peptide according to the presently claimed invention, are included among the drugs used in the disclosed combinations.

In contrast, the presently claimed invention relates to inclusion complexes solely formulated for oral administration. In view of the Examiner's admission that the compositions of FR '268 are specifically designed to "avoid problems of poor absorption after oral administration", it is not even possible that FR '268 could have recognized the oral dosage form required of the presently claimed inclusion complexes. Accordingly, the Examiner's arguments with respect to different motivation are moot in view of

his admission that the cited reference teaches away from the presently claimed orally efficacious inclusion complexes.

Additionally, applicants note that FR '268 teaches transcutaneous administration as an alternative to oral administration to "avoid problems of poor absorption after oral administration". However, since the publication of FR '268, several U.S. patents have been granted using cyclodextrin complexes with improved pharmacological activity (for example Hora et al. and Chiesi et al. cited by the Examiner, as well as Zmitak et al., U.S. Patent No.) using different well-defined and known substances for particular properties. Accordingly, the transdermal solution proposed by FR '268 does not always improve the pharmacological properties of a particular drug. In fact, several examples are available in the literature showing that the drug-cyclodextrin ration, stability constant of the complex, and dissolution properties of the complex differ on a case-to-case basis and are instead responsible for improvement in pharmacological properties.

For example, Uekema et al. (Drug Targeting Delivery 1994, 3, 411-456) reported that the largest impact of cyclodextrin on oral drug absorption results in an increased rate of dissolution of the drug complex, while the magnitude of the stability constant between the drug and cyclodextrin is dependent on absorption of the free uncomplexed drug through the GI mucosa.

Similarly, Szejtli (Cyclodextrin Technology, Davies J.E.D. ed., Kluwer Acad. Publ. Dordrecht 1988, pp. 186-306) provide a discussion and theoretical simulation showing the effect of the complexation stability constant and the ratio of drug to cyclodextrin on the blood level of the drug. When the stability constant of the complex is high or molar excesses of the complex in comparison with peak blood levels, the bioavailability attained may actually be lower for a formulation containing cyclodextrin relative to one containing only drug. Accordingly, the property of a cyclodextrin complex as such does not always improve its solubility absorption properties and bioavailability to the desired extent.

Rather, it is recognized that these improvements depend on the properties of the particular compound included in the complex, as well as the ratio of drug to complex. Accordingly, the Examiner's general conclusion that, for every drug, cyclodextrin complexation increases the stability, solubility, and bioavailability of the drug cannot properly be made. Accordingly, contrary to the Examiner's assertions, it is not obvious that the complexation of <u>any</u> basic drug or polypeptide with cyclodextrin will improve its solubility, stability, and bioavailability. It is the properties of the individual drug compound that decide their suitability for inclusion in cyclodextrin complexes. Accordingly, it would not

have been obvious to modify the teachings of FR '268 with the disclosure of the previously uncontemplated peptide disclosed by Nath et al. to arrive at the presently claimed invention. The presently claimed orally administered complexes of L-Tyr-D-Ala-Gly-N-methyl-Phe-Gly-NHC_3H_7 with β-cyclodextrin having a prolonged duration of action would not have been obvious in view of the cited references.

The Examiner has agreed on the record that each of Chiesi et al., Hora et al., EP '653, and FR '268 do not disclose the specific opioid peptide included in the present claims. In view of the Examiner's failure to provide a motivation to combine any of these references with the Nath et al. article, the present rejections represent an improperly broad reading of the non-obviousness requirement of 35 U.S.C. 103.

In fact, during the last two decades several permutations and combinations of different compounds/drugs with cyclodextrin have been tried and established for different activities, and patents (e.g. US 6,232,304; US 6,110,449; US 6,071,964; US 6,077,871; and US 5,866,179) have been granted in this regard after the publication of thousands of papers. None of these patents could possibly have been granted if the broad definition of obviousness presently asserted by the Examiner were the actual standard of obviousness. All of these patents were granted on the basis of a

new formulation of a cyclodextrin complex with a known drug having enhanced efficacy.

It is not at all obvious that cyclodextrin complexes will form with any compound, as alleged by the Examiner. Several parameters play a very crucial role in the formation of the complex. Some of these parameters include size of the drug molecule, polarity of the compound, and stability constant of the complex if formed. These are the properties of the individual drugs. All known drugs are not capable of forming cyclodextrin complexes. Further, the cyclodextrin complexes that are formed may have different properties, i.e. one cyclodextrin derivative can increase a particular effect while the other cyclodextrin derivative may reverse it. Accordingly, without some teaching in that general direction, it would not have been obvious to combine the disclosure of FR '268 with the previously uncontemplated compounds of Nath et al. to arrive at the presently claimed invention. FR '268 does not provide any such teaching. A person of ordinary skill in the art, then, would have had no motivation to combine the particular opioid peptide of Nath et al. with the FR '268 reference relating to a transdermal dosage form to arrive at the presently claimed orally administered inclusion complexes.

Regarding the Examiner's assertion that "the motivation used to combine the two references is the desirability of forming a

transcutaneously administrable composition comprising the compound of the Nath et al article", applicants respectfully reiterate that this combination is not the same as the presently claimed invention. In particular, the presently claimed invention relates to inclusion complexes formulated for oral administration. See claim 1. The combination suggested by the Examiner is transcutaneously, but not orally, administrable. Accordingly, the Examiner's proposed combination does not result in the same product as that which is presently claimed.

In making the present case of obviousness, the Examiner is using impermissible hindsight in theoretically combining the various prior art teachings to suggest the lack of inventiveness of the presently claimed invention. Science is not pursued in this manner. When there are contradictory results available in the prior art, then unless a person actually experiments with specific compounds, it is impossible to predict the results. If this were not the case, every invention would be theoretically imaginable, and therefore obvious. This clearly is not the current status of our law.

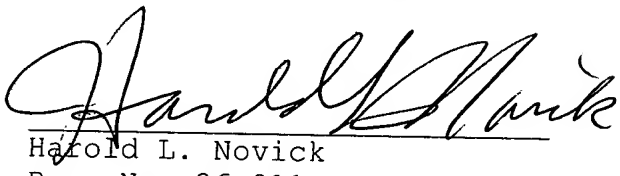
Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of FR '268 and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1, 8-9, 11, and 15.

CONCLUSION

In light of the foregoing, applicants submit that the application is now in condition for allowance. The Examiner is therefore respectfully requested to reconsider and withdraw the rejection of all pending claims 1-6, 8-9, 11, and 14-15 and allow these claims. Favorable action with an early allowance of the claims is earnestly solicited.

Respectfully submitted,

NATH & ASSOCIATES PLLC



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